Drug delivery to the inflammatory brain by enzyme responsive nanoparticles

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Aim

Drug delivery by nanoparticles requires that the particles can encapsulate and protect the drug during systemic circulation and then release the drug in the designated region. Qualities that support the first requirement often hamper the drug release and uptake in targeted cells. The purpose of this study is to design a delivery vehicle responsive to the specific enzyme environment of inflammatory- or stroke-affected brain so that the enzymatic activity triggers the exposure of a concealed cell penetrating peptide (CPP) for increased internalization and drug delivery.

- Material and methods:
  We have synthesized a lipopeptide composed of a cholesterol anchor and a poly(ethylene glycol) (PEG) segment linked by an amino acid sequence which contains a recognition site for matrix metalloproteinase (MMP). The responsiveness to enzyme activity of this PEGylated cleavable lipopeptide (PCL) was tested with HPLC and MALDI-TOF MS. Liposomes were formulated by hydration and extrusion of a lyophilized lipid mixture containing POPC and cholesterol together with a cholesterol anchored short cationic CPP. The PCL was then post-inserted into the liposomes and zeta-potential measurement was utilized to determine the surface charge of the liposomes before and after enzyme treatment. The responsiveness to MMP activity was also determined in barrier models by cell association studies of fluorescence labeled liposomes. To evaluate the drug delivery properties of the PCL liposomes we encapsulated the chemotherapeutic oxaliplatin and measured its cytotoxicity when delivered by enzyme responsive and non-responsive liposomes.

- Results
  The HPLC and MALDI-TOF analyses showed that the PCL was cleaved in the presence of MMP, both as a monomer and when incorporated into a liposome. For PCL incorporated into liposomes, the successful cleavage was confirmed by a change in surface charge following enzyme treatment. The PCL was designed with negative charges adjacent to the PEG polymer which gave the intact liposome a highly negative surface charge. After removal of the PEG-fraction and the negative charges, the underlying cationic CPP provided the liposomes with a net positive charge. The differences in surface charge had considerably influence on the cellular uptake of the liposomes as the PEGylated, negatively charged liposomes only had limited cell association while the enzyme-treated de-PEGylated and positively charged liposomes were rapidly internalized by the cells. In the cytotoxicity studies a similar behavior was observed as the oxaliplatin was more efficient delivered by MMP responsive liposomes.

- Conclusion
  The incorporation of PCL into the liposome formulation made the liposomes responsive to MMP activity. After enzyme treatment the liposomes shifted their surface charge from negative to positive and removed their protective PEG coating. This charge shift changed their interaction with cells to a much higher uptake and more efficient delivery of the drug.